Tet1 regulates adult hippocampal neurogenesis and cognition.

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Public Summary:
Neurons in the brain are generated from a pool of neural stem cells that have the ability to self-renew or to differentiate into mature neurons. It is critical that the brain both maintain this pool of self-renewing stem cells, yet also be able to activate these cells to undergo neurogenesis when needed. We have found that a protein called Tet1, which is involved in adding hydroxyl groups to methylated DNA, plays an important role in regulating the proliferation of neural stem cells in the adult mouse brain. Although DNA hydroxylation catalyzed by Tet dioxygenases occurs abundantly in embryonic stem cells and neurons in mammals, its biological function in vivo has been largely unknown. We found that mice that lacked a Tet1 gene had impaired neurogenesis in the hippocampus, a region of the brain important for learning and memory. Not surprisingly, these mice also had poor learning and memory. In addition, expression of a cohort of genes involved in proliferation of neural stem cells was downregulated in adult neural stem cells that were deficient in Tet1. Our results indicate that Tet1 is positively involved in regulating proliferation of neural stem cells in the adult brain. Thus, this study could have implications for improving our ability to expand or maintain pools of neural stem cells, or to trigger these cells to differentiate.

Scientific Abstract:
DNA hydroxylation catalyzed by Tet dioxygenases occurs abundantly in embryonic stem cells and neurons in mammals. However, its biological function in vivo is largely unknown. Here, we demonstrate that Tet1 plays an important role in regulating neural progenitor cell proliferation in adult mouse brain. Mice lacking Tet1 exhibit impaired hippocampal neurogenesis accompanied by poor learning and memory. In adult neural progenitor cells deficient in Tet1, a cohort of genes involved in progenitor proliferation were hypermethylated and downregulated. Our results indicate that Tet1 is positively involved in the epigenetic regulation of neural progenitor cell proliferation in the adult brain.